

Nervous control of reproduction in *Octopus vulgaris*: a new model

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Abstract The classic study of Wells and Wells on the control of reproduction in *Octopus* demonstrated that the activity of the subpedunculate lobe of the brain and environmental illumination both inhibit the release of an unknown gonadotropin from the optic gland. This inhibitory control may be exerted by the neuropeptide Phe-Met-Arg-Phe-NH₂ (FMRFamide). It was later demonstrated that the olfactory lobe is also likely to be involved in the control of optic gland activity. The presence of gonadotropin-releasing hormone in the olfactory lobe suggested that it might exert an excitatory action on optic gland activity. Other neuropeptides have now been localised in the olfactory lobe: neuropeptide Y, galanin, corticotropin-releasing factor, Ala-Pro-Gly-Trp-NH₂ (APGWamide), as well as steroidogenic enzymes and an oestrogen receptor orthologue. This supports the hypothesis that this lobe may also play a part in the control of reproduction in *Octopus*. The olfactory lobe receives distant chemical stimuli and also appears to be an integrative centre containing a variety of neuropeptides involved in controlling the onset of sexual maturation of *Octopus*, via the optic gland hormone. This review attempts to summarise current knowledge about the role of the olfactory lobe and optic gland in the control of

sexual maturation in *Octopus*, in the light of new findings and in the context of molluscan comparative physiology.

Keywords Cephalopod · Octopus · Reproduction · Neuropeptides · Metabolism · Steroids

Introduction

The growth and functional maturation of the gonads in many invertebrates, as well as vertebrates, depends on the action of gonadotropic hormones (Engelmann 1994). These are generally synthesised and released by endocrine glands, although in invertebrates they are often released from neurons. In the classical concept of input–output relations, regions in the nervous system receive and integrate coded external stimuli (inputs such as temperature changes, photoperiod, food intake and partner availability) to generate internal responses that affect endocrine glands and, subsequently, gonad growth and maturation, egg laying, sexual behaviour (outputs).

In many invertebrates, the activity of endocrine glands involved in sexual maturation is negatively controlled by the nervous system (Engelmann 1994). Generally, neurons produce factors that block gonadotropin release by endocrine cells unless coordinated (from different lobes) and synergistic inputs (time-linked) would reverse such inhibition by either shutting down a negative control or turning on a positive one.

The onset of sexual maturity in cephalopods seems to be controlled in this way: the subpedunculate lobe negatively controls the activity of the optic gland, which is assumed to release an as yet unidentified gonadotropic hormone (Wells and Wells 1959). However, is that sufficient to regulate sexual maturation in *Octopus*?

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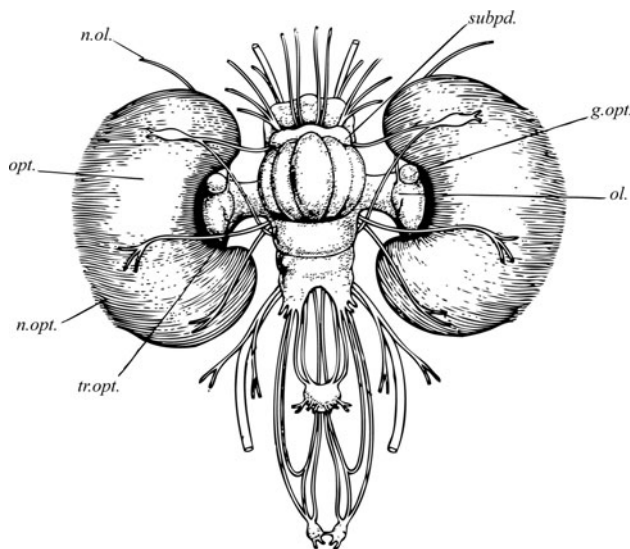


Fig. 1 Diagrammatic drawing of *Octopus* CNS as seen from above (modified from Young 1971). *g.opt.* optic gland, *n.ol.* olfactory nerve, *n.opt.* optic nerves, *ol.* olfactory lobe, *opt.* optic lobe, *subpd.* subpedunculate lobe, *tr.opt.* optic tract

The subpedunculate lobe

Cephalopod optic glands are endocrine organs lying on the optic tracts (Fig. 1): they control the maturation of the reproductive system. In *Octopus vulgaris*, cutting the optic tract results in hypertrophy of the optic gland and gonadal maturation (Boycott and Young 1956). Wells and Wells (1959) hypothesised that optic glands secrete a gonadotropic hormone and clarified the relationship between the gland and the central nervous system (CNS). They demonstrated that either cutting the optic gland nerve or making a surgical lesion in the subpedunculate lobe resulted in an enlargement of the gland and a subsequent hypertrophy of the gonads. A similar response, although weaker, is produced by cutting the optic nerves or removing the optic lobes. They therefore proposed that the CNS exerts an inhibitory control on the optic gland via the optic gland nerve and that photoperiod also plays a crucial role in controlling gonad maturation: darkness activates it.

Ultrastructural analyses of the optic glands (Bjorkman 1963) revealed that, in the immature optic gland, there are two types of synapses, axoaxonal (among fibres of optic gland nerve) and axoglandular (contacts on glandular chief cells), whereas there is only one type of synapse, the axoglandular, in the mature gland (Froesch 1974). It was proposed that the axoaxonal synapses might inhibit the axoglandular synapses, according to the widespread pattern of presynaptic inhibition (Froesch 1974). This idea was supported by the absence of axoaxonal synapses in the gland of adult animals, which is supposed to be active only in the absence of inhibition.

In a study of the neuropeptidergic innervation of the optic gland of *Sepia*, Le Gall et al. (1988) found that the neuropeptide Phe-Met-Arg-Phe-NH₂ (FMRFamide) is the substance present in the optic gland nerve that inhibits the activity of the gland. Later, it was demonstrated that in *Octopus*, too, the optic glands are innervated by FMRFamide immunoreactive fibres originating from neurons in both the subpedunculate and the olfactory lobes (Di Cosmo and Di Cristo 1998).

The olfactory lobe

In *Octopus*, the olfactory lobe lies on the optic tract, close to both the peduncle lobe and the optic gland and is subdivided into three lobules (anterior, middle and posterior) (Young 1971; Messenger 1967; Fig. 1). The name of this lobe comes from its connection, through the olfactory nerve, to the olfactory organ, a chemoreceptor organ (Woodhams and Messenger 1974) whose function, at least in *Octopus*, is still far from clear. It should be emphasized that in *Octopus*, which uses its arms for detecting food, there are millions of chemoreceptors on the suckers (Graziadei 1964). The role of olfactory organs and olfactory lobes is therefore presumably related to distance chemical reception (olfaction), rather than chemotactile perception, via the suckers (taste by touch, Wells 1962; see also Hanlon and Messenger 1996). The presence in this lobe, particularly in the posterior lobule of peptidergic neurons that innervate optic gland cells, has led to a critical revision of the role played by the olfactory lobe in reproduction (Di Cosmo and Di Cristo 1998). The mediator of this new control is probably gonadotropin-releasing hormone (GnRH), a neuropeptide belonging to the family of gonadotropin-releasing hormone of vertebrates (Millar 2005). Neurons containing this neuropeptide send their axons to the chief cells of optic gland (Di Cosmo and Di Cristo 1998; Iwakoshi et al. 2002; Iwakoshi-Ukena et al. 2004). Whether this neuropeptide affects reproduction in *Octopus*, however, is still an open question. Some cues favour such a hypothesis, but others, coming from comparative studies, seem to exclude a direct role of GnRHs in reproduction in molluscs.

Octopus GnRH

The octopus GnRH dodecapeptide (octGnRH) is a member of the wide family of gonadotropin-releasing hormone neuropeptides, which in vertebrates are essentially involved in the activation of gonadotropin release from the pituitary gland (Morgan and Millar 2004). The ancient origin of this

peptide was suggested by the recent description of orthologues of GnRH in many invertebrates, including non-vertebrate chordates (Tsai and Zhang 2008; Roch et al. 2011). In molluscs, GnRH has been sequenced in three cephalopods (Iwakoshi et al. 2002; Di Cristo et al. 2009; Onitsuka et al. 2009), two bivalves (Bigot et al. 2012; Treen et al. 2012) and two gastropods (Tsai and Zhang 2008; Zhang et al. 2008). The presence in the nematode *Caenorhabditis elegans* of a peptide with the structural features of both GnRH and insect adipokinetic hormone (termed GnRH-AKH) (Lindemans et al. 2009) possibly suggests the presence of a GnRH peptide superfamily (Roch et al. 2011).

In contrast to the sequence elucidation of GnRHs, very few functional data are available in molluscs. Many studies have been performed primarily using vertebrate GnRH peptide isoforms (Goldberg et al. 1993; Pazos and Mathieu 1999; Young et al. 1999; Zhang et al. 2000; Gorbman et al. 2003; Nakamura et al. 2007), complicating data interpretation. To date, physiological studies based on homologous GnRH administration have been conducted on few species. In *Octopus vulgaris*, octGnRH stimulates oviduct contraction and gonadal steroidogenesis, suggesting a role in the reproductive process (Iwakoshi-Ukena et al. 2004; Kanda et al. 2006). In *Aplysia*, however, homologous GnRH has little effect on the activation of reproduction, although it modulates the activity of diverse central neurons and inhibits after discharge in bag cells (Tsai et al. 2010; Sun and Tsai 2011). Finally, putative scallop GnRH-like peptide stimulated spermatogonial cell division in cultured scallop testis (Treen et al. 2012).

Interestingly, in *Caenorhabditis elegans*, although homologous peptide administration was not performed, RNA interference that disrupted the production of GnRH-AKH prohormone resulted in delayed egg laying (Lindemans et al. 2009).

This mismatch between structure and function in GnRH in invertebrates has no simple explanation and we should probably ask why reproduction seems to be affected by GnRH only in some species. One possible line of enquiry that could help in addressing this problem would be to study the presence, expression, pharmacology and physiology of GnRH receptors in invertebrates. In *Octopus*, a GnRH receptor has been identified and characterised (Kanda et al. 2006). This receptor is distributed throughout nervous and peripheral tissues, and interestingly in the olfactory lobe, optic gland, as well as in the gonads. It responds specifically to its native peptide (octGnRH) to activate the classical GnRH-induced signal transduction pathway; this results in steroidogenesis in reproductive tissues during bioassays (Kanda et al. 2006). However, without data on the octopus gonadotropin, it is impossible to define the role of GnRH in the release of gonadotropin in *Octopus*.

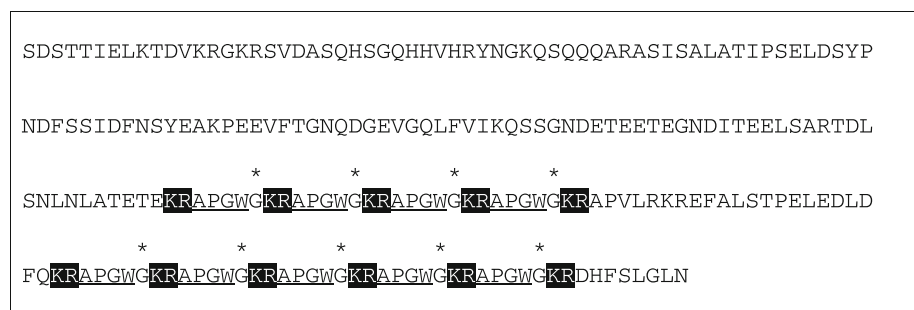
Other neuropeptides

In addition to GnRH and FMRFamide, the olfactory lobe also contains several peptides. Immunoreactive-like signals for galanin (Suzuki et al. 2000), neuropeptide Y (NPY; Suzuki et al. 2002), corticotropin-releasing factor (CRF; Suzuki et al. 2003) and Ala-Pro-Gly-Trp-NH₂ (APGWamide; Di Cristo et al. 2005) have been reported in *Octopus vulgaris*. Some of these results are exclusively based upon immunological data and need to be supported by strong molecular data, but an APGWamide mRNA is present in the transcriptome of *Octopus* CNS (Fig. 2; Zhang et al. 2012) and a nonapeptide, designated peptide tyrosine phenylalanine (PYF) was isolated from brain of the squid *Loligo vulgaris* (Smart et al. 1992). This peptide shows high homology with the C-terminal end of the other molluscan NPYs (7 out of 9 residues are identical) and could be a processed form of a genuine squid NPY neuropeptide.

Galanin (and galanin-like peptides), NPY and CRF, whose presence in the olfactory lobe has been hypothesised, play important roles in the balance between metabolism and reproduction not only in vertebrates (Crown et al. 2007), but also in invertebrates (see de Jong-Brink et al. 2001 for the role of NPY in invertebrates). In particular, in vertebrates: (i) neuropeptides, including galanin-like peptide (GALP), NPY, products of the proopiomelanocortin, whose release depends on CRF, all reside in the hypothalamic area involved in the regulation of both metabolism and reproduction; (ii) neurons producing these peptides are the targets of metabolic hormones, such as leptin and insulin, and (iii) these neuropeptide either directly or indirectly affect feeding and metabolism, as well as the secretion of GnRH and gonadotropins.

APGWamide is a typical molluscan-amidated tetrapeptide, which essentially plays a key role in male sexual behaviour in gastropods (de Lange and Joosse 1998; de Lange and van Minnen 1998). The presence of this neuropeptide in the olfactory lobe of *Octopus*, which receives and processes distant chemosensory information (olfaction sense) (Hanlon and Messenger 1996; Young 1971), supported the fascinating hypothesis that in cephalopods olfaction could mediate the aspects of sexual behaviour (Di Cristo et al. 2005). At the moment, however, there is still no experimental evidence that the action of such pheromones is via the olfactory organ. However, a waterborne pheromonal attractant has been purified from egg mass of *Sepia officinalis* (Zatylny et al. 2000) and waterborne pheromonal peptides are present in the *Aplysia* (Cummins et al. 2008). Interestingly, in *Octopus*, APGWamide is also present in the inferior frontal system, which receives chemotactile inputs from suckers. In *Loligo*, chemotactile

Fig. 2 Aminoacidic sequence of pre-pro-APGWamide peptide from contig JR446524 of *Octopus* transcriptome (Zhang et al. 2012). Copies of APGWamide are underlined and glycine residues required for C-terminal amidation are marked by asterisks. Dibasic cleavage sites are highlighted



inputs evoke the intra-male competition for mates (Buresch et al. 2004) and, in *Octopus*, relatively quiet males become highly active as females touch them or vice versa. This observation of mating behaviour in octopuses suggests that physical and probably chemical contact might play a part in sex recognition (Hanlon and Messenger 1996).

Steroids

Sex steroids are key molecules in the endocrine mechanisms of vertebrates (Bentley 2001). In many invertebrates, mainly molluscs, “vertebrate-like sex steroids” were essentially believed to act as endocrine disruptors (Lafont and Mathieu 2007). However, the discovery that these animals synthesise steroids and show tissue expression of steroid receptors has resulted in a reconsideration of the role these molecules play in invertebrate reproduction (Kohler et al. 2007).

Recently, many data on the presence of steroids in *Octopus vulgaris* have been produced (D’Aniello et al. 1996; Di Cosmo et al. 1998, 2001; Tosti et al. 2001; Di Cosmo et al. 2002; Cuomo et al. 2005; Di Cristo et al. 2008, 2010; De Lisa et al. 2012). These papers cover the biochemistry, physiology and pharmacology of vertebrate-like sex steroids in this species and establish three key points: (i) *Octopus* can synthesise steroids in both the gonads and the brain; (ii) these steroids interact with specific receptors localised in the gonads, reproductive tracts and in specific brain regions; and (iii) these steroids can affect the physiology of the gametes.

Of particular interest is the presence of an orthologue of the oestrogen receptor (octER) in the olfactory lobe (De Lisa et al. 2012). This receptor, when recombinantly expressed and purified, is able to bind oestradiol pending conformational changes (De Lisa et al. 2012). In fact, previous findings reported the same receptor was unable to bind 17 β -oestradiol (Keay et al. 2006). Interestingly, stimulation with 17 β -oestradiol increases the octGnRH transcript, as well as the octER transcript, in the olfactory lobes (De Lisa et al. 2012). This result links the expression of GnRH in the olfactory lobe

to the presence of oestrogens, whose level fluctuates throughout the entire life cycle of, at least, the female of *Octopus* (Di Cosmo et al. 2001), peaking just before egg laying. It is noteworthy that the level of octER gene in the olfactory lobe also fluctuates (personal observations).

Revisiting the nervous control of *Octopus* reproduction

Old models

The fascinating discoveries of Wells and Wells (1959) remain the basis of our understanding of the neuroendocrine control of reproduction in *Octopus* even after half a century (Fig. 3a). Wells later attempted to extend his findings by adding molecular data (O’Dor and Wells 1973, 1975; Wells et al. 1975; Wells and Wells 1975), but was unable to purify the gonadotropic hormone from the optic gland, which led him to abandon this area of research.

Recent data suggest that the olfactory lobe as well as the subpedunculate lobe is involved in the control of the activity of the optic gland (Di Cosmo and Di Cristo 1998). These data led to the neuroanatomical evidence that the olfactory lobe might influence the optic gland by releasing a positive factor (GnRH?) to counterbalance the inhibitory effect of FMRFamide from the subpedunculate lobe on the glandular cells. This model, consisting of two centres controlling the activity of the optic gland, constitutes a simple feedback loop to switch optic gland activity on and off (Fig. 3b).

Anatomical data further support the hypothesis these two lobes are coupled in the control of optic gland activity. Embryologically, they both derive from the dorsal part of supraesophageal mass of *Octopus* brain. This is clearly evident in decapods like *Sepia* and *Loligo*, where the neuropils of the olfactory and dorsolateral lobe are continuous (Boycott 1961; Messenger 1979).

Even if the “two centres” model is validated, however, far more details are required to complete it. We need to know what activates the switch; and above all, we need to know what the optic gland hormone actually does?

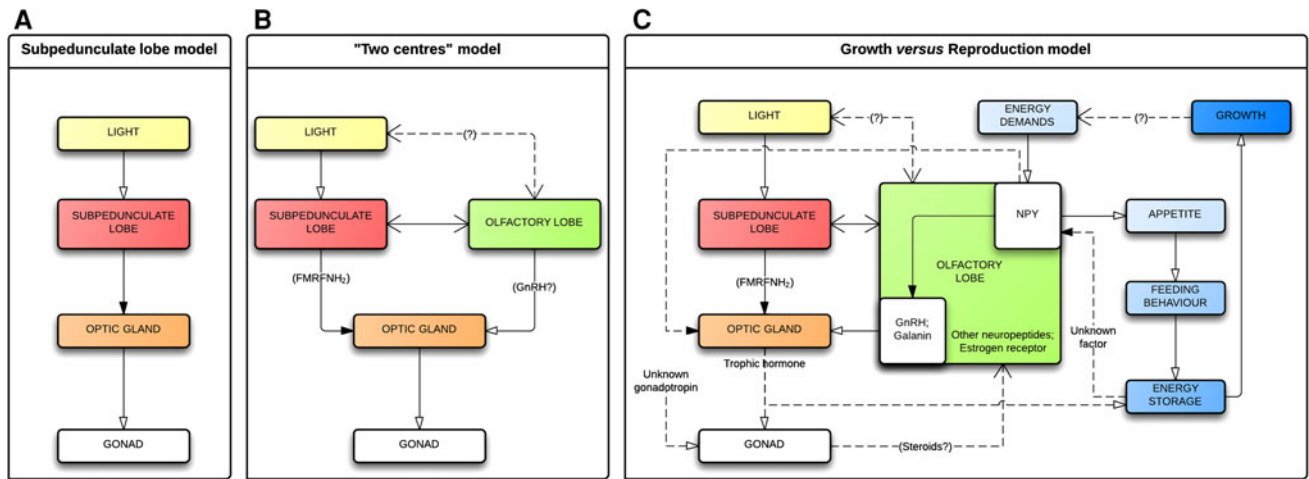


Fig. 3 Schemes of the relevant structures involved in the nervous control of *Octopus* reproduction. **a** Model proposed by Wells and Wells 1959. **b** Model proposed by Di Cosmo and Di Cristo 1998. **c** Model proposed in the present paper. *Black arrowheads* represent

inhibitory control; *white arrowheads* represent excitatory control; *arrows* represent unknown relationships. *Dashed lines* indicate supposed pathways

Growth versus reproduction model

Incidentally, the neuropeptides that are present in the olfactory lobe are involved in the neurocoding of inputs about the state of stored energy by the animal, possibly from food intake. NPY in the gastropod *Lymnaea stagnalis*, for example, is involved in regulating energy flow (de Jong-Brink et al. 2001). Although it does not affect food intake, it may stop the main energy consuming processes, like reproduction. When infected by endoparasites, the NPY gene in *Lymnaea* is up-regulated, causing egg laying to stop immediately (de Jong-Brink et al. 1999).

In all animals, the energy demands of reproduction mean that the nervous system must temper the fertility of individuals to match nutritional availability. *Octopus* is no exception and its feeding behaviour is obviously linked to reproduction. Females reproduce only once and their large eggs require their converting energy from food into the large amount of yolk filling the eggs. This process depends on the optic gland hormone (O’Dor and Wells 1973). Moreover, during egg laying and egg care, they stop feeding and death comes soon after hatchlings (Wells 1978). This semelparous behaviour, as well as the ensuing death, also seems to be controlled by the optic gland hormone (Wodinsky 1977). According to these data, optic gland hormone shifts the balance from general body growth to reproduction (O’Dor and Wells 1978).

In order to propose a new scheme of nervous control of reproduction in *Octopus* (Fig. 3c), one could suggest that during initial life stages (Di Cosmo et al. 2001), NPY neurons “perceive” the energy demands. They could then affect feeding behaviour and, at the same time, shut down optic gland activity, possibly in coordination with the

subpedunculate lobe, by negatively modulating the activity of GnRH neurons. This would shift energy to body growth rather than reproduction.

When internal signals of satiation indicate that a discrete level of energy stored is reached and can be converted into yolk, these inputs could inhibit NPY neurons. This would release from inhibition those neurons activating optic gland (GnRH?; Galanin?) and stop the activity of the subpedunculate lobe. Vitellogenesis could then be initiated and the energy flow shifted to vitellogenesis and gonadal maturation.

Such a process could be affected also by sex steroids, as well as their receptors, whose levels fluctuate during the life cycle (Di Cosmo et al. 2001). The role of oestrogen receptor in *Octopus* is still unclear (Keay et al. 2006; De Lisa et al. 2012), but the absence of “vertebrate” steroidogenic enzymes in molluscs (Markov et al. 2009) might suggest that this receptor in the olfactory lobe (De Lisa et al. 2012) works as a sensor, binding at low affinity the different hydrophobic molecules in the diet (Markov and Laudet 2011). If so, the pathway mediated by this receptor would be influenced by the “metabolic milieu.”

The whole hypothetical scenario implies that there is an unknown factor that signals the “state of satiety.” Its release positively depends on the optic gland hormone titre.

Optic gland hormone

The most intriguing aspect of this topic concerns the optic gland hormone: is it a gonadotropin affecting gonad maturation, gametogenesis and egg laying? Or more probably is it a trophic hormone, which only induces gonad ripening and vitellogenesis, as in gastropods, where

dorsal bodies have this function (Roubos et al. 1980). Nonetheless, Wells and Wells (1959) reported that only three of sixty-nine females with optic gland-activating lesions lobe laid eggs.

This fascinating suggestion obviously poses another question: what is the hormone responsible for gametogenesis and egg laying in *Octopus*? Is there an octopus gonadotropin hormone like the egg-laying hormone in *Aplysia* or the caudodorsal cells hormone in *Lymnaea* (Di Cosmo and Di Cristo 2006)? And where is released from?

Such a suggestion would give possible answers about the control of male sexual maturation. In fact, this unknown hormone could justify why *Octopus* males produce mature spermatophores long before optic gland enlargement (O'Dor and Wells 1978). It can be inferred that in males, the continued production of spermatozoa in young males probably does not rely on a high-energy requirement. This would imply that the trophic optic gland hormone is not needed, confirming the existence of another hormone regulating gametogenesis and gamete release.

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Conflict of interest None.

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